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Digital arterial pressure pulse wave analysis and cardiovascular events in the general population: the Prevention of Renal and Vascular End-stage Disease study

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Background: Arterial stiffness influences the contour of the digital pressure pulse wave.

Method: Here, we investigated whether the digital pulse propagation index (DPPI), based on the digital pressure pulse wave, DPPI is associated with cardiovascular events, heart failure, and mortality in a large population-based cohort. Between 2001 and 2003, DPPI was measured with a PortaPres noninvasive hemodynamic monitoring device (FinaPres Medical Systems, Amsterdam, The Netherlands) in participants of the Prevention of Renal and Vascular End-stage Disease study, a community-based cohort. We assessed the main determinants of the DPPI and investigated associations of DPPI with cardiovascular events and mortality.

Results: The study included 5474 individuals. Mean age was 52.3 ± 11.8 years and 50.5% was male. Median baseline DPPI was 5.81 m/s (interquartile range 5.47–6.20). Higher age, mean arterial blood pressure, body height, heart rate, current smoking, and lower HDL cholesterol levels and waist circumference were independent determinants of the DPPI ($r^2 = 0.43$). After adjustment for heart rate, high$_{log}$DPPI was associated with all-cause mortality [hazard ratio: 1.67, 95% confidence interval (1.55–1.81) per SD; $P < 0.001$], cardiovascular mortality [hazard ratio 1.95 (1.72–2.22); $P < 0.001$], and incident heart failure with reduced ejection fraction [hazard ratio 1.81 (1.60–2.06); $P < 0.001$]. These associations remained independent upon further adjustment for confounders. Optimal cutoff values for DPPI ranged between 6.1 and 6.3 m/s for all endpoints. After multivariable adjustment, DPPI was no longer associated with coronary artery disease events or cerebrovascular events.

Conclusion: The DPPI is associated with an increased risk of development of new onset heart failure with reduced ejection fraction and all-cause and cardiovascular mortality, but not with coronary artery events or cerebrovascular events.

Keywords: heart failure, mortality, pulse contour analysis, risk factors

Abbreviations: AUC, area under the curve; CAD, coronary artery disease; cfPWV, carotid–femoral pulse wave velocity; CVD, cardiovascular disease; DPPI, digital pulse propagation index; DVP, digital volume pulse; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, International Statistical Classification of Diseases and Related Health Problems; IQR, interquartile range; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; PPT, pulse propagation time; PREVEND, Prevention of Renal and Vascular End-stage Disease; UAE, urinary albumin excretion per 24 h

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide [1]. Large artery stiffness is a hallmark of vascular aging, and may be a consequence of pathological processes including hypertension. Increased arterial stiffness is associated with cardiovascular risk factors, morbidity [2–4], and mortality [2,4–6]. Hence, the early detection of arterial stiffening may contribute to the identification of high-risk patients, and may thereby improve prevention of CVD [7,8].

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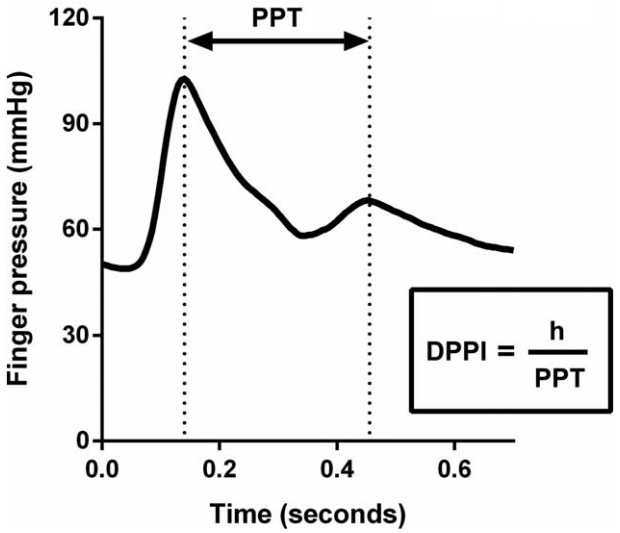

FIGURE 1 The digital pulse waveform consists of a direct pressure wave traveling directly from the heart to the finger, and a second wave which is reflected from the resistance arteries in the lower body. Digital pulse propagation index is calculated by dividing the height of a patient (*h*) by the difference in arrival time (pulse propagation time) between this first and second wave.

Digital pulse wave analysis is a technique that intends to assess arterial stiffness using the peripheral arterial pulse waveform. This waveform can be measured from a finger, using photoplethysmography or a pressure sensor [9–11]. Here, we obtained digital finger pressure pulse data, which can subsequently be used to derive the pulse propagation time (PPT), defined as the time between the systolic and diastolic peak (Fig. 1) [9]. Finally, the digital pulse propagation index (DPPI, expressed in meter per second) can be calculated by dividing the height of each individual by the PPT [9]. DPPI Previous studies have shown that digital volume pulse (DVP) analysis, which is a slightly different method based on photopletysmography, has a low failure rate and good within-individual repeatability [12,13] and has been correlated with individual cardiovascular risk scores [12–14]. Digital pulse wave measurement is relatively simple, rapid and requires no special training [8–10].

However, it remains unclear whether DPPI is a predictor of cardiovascular outcomes. While pulse contour analysis initially appeared to correspond closely with the gold standard of arterial stiffness measurement, carotid–femoral pulse wave velocity (cfPWV) [10,13], later studies only observed a weak association between these methods [15]. Although cfPWV has been clinically validated, prospective data on associations between DPPI and cardiovascular morbidity and mortality are sparse.

Here, we investigated potential associations between the pulse contour-based DPPI, measured using a pressure sensor (PortaPres), and cardiovascular outcomes in the general population-based Prevention of Renal and Vascular End-stage Disease (PREVEND) cohort.

METHODS

Study population

The study was performed using the data of the PREVEND cohort study, which has been described elsewhere [16]. In summary, between 1997 and 1998, all inhabitants of the city of Groningen, The Netherlands, aged 28–75 years ($N = 85\,421$) were asked to send in a first morning urine sample and a short questionnaire on demographics and CVD history. 40 856 individuals responded (47.8%). All individuals with urinary albumin excretion (UAE) more than 10 mg/l ($N = 7786$) in the urine sample and a randomly selected control group with a UAE less than 10 mg/l ($N = 3395$) were invited to an outpatient clinic for a detailed assessment of cardiovascular and renal risk factors, including filling in questionnaires, measuring anthropometrics, and blood and urine sampling. After excluding individuals with insulin-dependent diabetes mellitus, pregnant women, and individuals unable or unwilling to participate, a total of 8592 individuals completed the screening.

Between 2001 and 2003, 6894 individuals of the PREVEND study participated in a follow-up examination. At this time, the DPPI was measured in 5487 participants using pulse contour analysis. This subcohort was used for the present analysis. The PREVEND study was approved by the medical ethics committee of the University Medical Center Groningen and abides to the principles of the Declaration of Helsinki.

Digital pulse propagation index measurement

The DPPI was measured from the middle finger for 15 min in supine position, using a Portapres finger blood pressure (BP) monitor and Beatscope software (Finapres Medical Systems, Amsterdam, The Netherlands). This system uses a servo-system to continuously register the digital finger pressure pulse [17]. We subsequently analyzed the pulse wave to derive PPT, defined as the time between the systolic and diastolic peak, as described by Millasseau *et al.* [9]. The DPPI, expressed in meter per second, was calculated by dividing the height of each individual by the PPT [9]. The intra-individual coefficient of variation of DPPI assessment over the 15 min of measurement was 4.1%.

Assessment of endpoints

Data on hospitalization for nonfatal CVD were obtained from the Dutch national registry of hospital discharge diagnoses. Coronary artery disease (CAD) events and cerebrovascular events were coded according to International Statistical Classification of Diseases and Related Health Problems (ICD)-10. CAD events were defined as myocardial infarction, a diagnosis of ischemic heart disease, coronary artery bypass grafting or percutaneous transluminal coronary angioplasty. Cerebrovascular events were defined as intracranial hemorrhages, occlusion and stenosis of cerebral precerebral arteries, or carotid desobstruction. Both fatal and nonfatal events were scored. New onset heart failure [with either reduced (HFrEF, left ventricular ejection fraction (LVEF) $\leq 40\%$) or preserved (HFpEF, LVEF $\geq 50\%$) ejection fraction] were identified by an adjudication committee in accordance with the guidelines of the European Society of Cardiology, as published previously [18]. Mortality data were obtained through the municipal register. Cause of death was classified using the primary cause of death as listed on the death certificate using ICD-10. Person-time was calculated from the date of DPPI measurement and the date of death. Surviving patients were censored based on the date of the last attended follow-up visit.

Assessment of covariates

BP was measured on the right arm, in supine position, every minute for 10 min, using an automatic Dinamap XL Model 9300 series device (Johnson-Johnson Medical, Tampa, Florida, USA). The mean of the last two recordings was used to calculate the mean arterial BP (MAP). Participants collected two 24-h urine samples. UAE was determined by nephelometry (Dade Behring Diagnostic, Marburg, Germany). Urine sodium excretion was measured with a MEGA clinical chemistry analyzer (Merck, Darmstadt, Germany). Plasma HDL and total cholesterol, triglycerides, N-terminal-pro brain natriuretic peptide (NT-proBNP) and serum glucose and creatinine were measured on a Roche Modular analyzer (Roche Diagnostics, Mannheim, Germany).

Self-administered questionnaires were used to assess demographics, cardiovascular and renal medical history and family history, medication use, ethnicity, smoking status, alcohol consumption, and attained education [16]. Data on medication use was complemented with information from community pharmacies (with complete medication records of >90% of participants) [19]. Smoking status was categorized as never, former, and currently smoking. Type 2 diabetes mellitus was defined as a fasting plasma glucose more than 7.0 mmol/l, a nonfasting plasma glucose more than 11.1 mmol/l, or use of antidiabetic medication. Estimated glomerular filtration rate (eGFR) was calculated using the creatinine-based Chronic Kidney Disease-Epidemiology collaboration (CKD-EPI) equation, which also includes variables for age, sex, and ethnicity. Missing data on covariates (number of cases: cholesterol: 226, NT-ProBNP: 165, eGFR: 164, waist circumference: 22, urine albumin excretion: 124) were handled using multiple imputation.

Statistical analysis

Data are shown as mean and SD or median and interquartile range (IQR) for skewed distributed variables. Categorical variables are shown as total and percentage. The DPPI was log 10-transformed for all analyses. Covariates with skewed distributions were log-transformed when appropriate. Differences in baseline variables across these quartiles were assessed using analysis of variance (ANOVA), Kruskal–Wallis, and Chi-squared tests. Univariable and subsequent multivariable linear regression was used to assess likely determinants of the DPPI.

Cox proportional hazards models were subsequently used to estimate hazard ratios for the outcomes of interest based on the $_{log}$DPPI. Harrell's *C* was calculated as a measure of goodness of model fit. The initial model was adjusted for heart rate (HR) (model 1), and subsequent models were additionally adjusted for age, sex, and body height (model 2), MAP, use of antihypertensive drugs, smoking, prior history of CVD and NT-proBNP (model 3), and lastly for waist circumference, HDL cholesterol, triglycerides, presence of diabetes mellitus, eGFR, UAE, and urinary sodium excretion (model 4). Independent associations between $_{log}$DPPI and outcomes were subsequently investigated again after exclusion of participants with a history of CVD, using the fully adjusted model (model 4). To visualize significant associations between the DPPI and outcomes, restricted cubic splines were generated with knots placed at the 10th, 50th, and 90th percentile. Receiver operating characteristic (ROC) curves were used to identify the optimal cutoff values for DPPI based on Youden's J statistic (sensitivity + specificity − 1) [20]. Multiplicative interaction terms and effect modification was used to explore the consistency of the association between the DPPI and mortality. The investigated potential effect modifiers were relevant correlates of DPPI, identified by the prior linear regression analysis, as well as clinically relevant covariates. For this purpose, continuous variables were dichotomized based on clinically relevant cutoff values.

Statistical analyses were performed using SPSS version 23.0 (SPSS, Inc. Chicago, Illinois, USA). For all tests, a two-sided *P* value of less than 0.05 was regarded as statistically significant. Figures were generated using Graphpad version 6 (GraphPad Software, San Diego, California, USA). Restricted cubic spline fitting was performed with R 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Mean age of the 5487 PREVEND participants in our study was 52.3 ± 11.8 years and 50.6% were male. The majority of the cohort (96.1%) was of white descent. Median baseline DPPI was 5.81 m/s (IQR 5.47–6.20). The distribution of DPPI was skewed to the right. Baseline characteristics of the cohort per quartile of DPPI are presented in Table 1. Participants with high DPPI were older ($P < 0.001$) and more likely to be male (<0.001). In addition, high DPPI was associated with established cardiovascular risk factors, including mean arterial BP (MAP) and smoking (all $P < 0.001$).

Associations between potential determinants and $_{log}$DPPI were further explored using multivariable linear regression analysis (Table 2). Higher age, higher MAP, greater length, higher HR, active smoking, male sex, and lower HDL cholesterol levels were all associated with a higher DPPI. The resulting model explained 43% of the variance in DPPI. In multivariable models adjusted for age sex and height, diastolic blood pressure (DBP) was more strongly associated with MAP (β 0.342) or DBP (β 0.362) than with SBP (β 0.265), and was only weakly associated with pulse pressure (PP) (β 0.078; Supplemental Table 1, http://links.lww.com/HJH/B279).

Digital pulse propagation index and mortality

During a median follow-up of 8.3 (IQR 7.7–8.9) years, 289 (5.3%) participants died, of whom 74 (1.3%) of cardiovascular causes. Participants who died had a higher DPPI than those who did not (5.78 [5.46–6.62] vs. 6.30 m/s [5.83–6.78]; $P < 0.001$). Cox regression analysis showed a significant association between $_{log}$DPPI and the risk of both all-cause [hazard ratio 1.67 (1.55–1.81) per SD change, $P < 0.001$] and cardiovascular mortality [hazard ratio 1.95 (1.72–2.22) per SD change, $P < 0.001$; Fig. 2]. Both associations remained significant after multivariable adjustment for potential confounders (Table 3). In the fully adjusted model, each SD increase in $_{log}$DPPI was associated with a 14% greater risk of all-cause mortality and with a 45% greater risk of cardiovascular mortality. The optimal cutoff value for DPPI in relation to all-cause mortality was 6.2 m/s [area under the curve $(AUC)_{ROC}$: 0.70; sensitivity: 55%; specificity: 79%]. For cardiovascular mortality, the optimal cutoff value was 6.3 m/s (AUC_{ROC}: 0.75; sensitivity: 64%; specificity: 80%).

TABLE 1. Baseline characteristics according to quartiles of digital pulse propagation index

	Full cohort	Quartile 1 <5.47 m/s	Quartile 2 5.47–5.81 m/s	Quartile 3 5.81–6.20 m/s	Quartile 4 >6.20 m/s	*P* value
Participants, *n*	5487	1371	1372	1372	1372	
DPPI (mean over 15 min)	5.81 [5.47–6.20]	5.22 [5.11–5.36]	5.64 [5.56–5.72]	5.98 [5.89–6.08]	6.55 [6.34–6.90]	
Men (%)	50.6	19.8	47.9	65.2	69.8	<0.001
Age (years)	52.3 ± 11.8	47.1 ± 10.3	49.7 ± 11.1	52.9 ± 11.3	59.4 ± 11.0	<0.001
Waist circumference (cm)	91.9 ± 12.6	86.3 ± 12.6	89.8 ± 11.7	93.9 ± 11.5	97.4 ± 11.8	<0.001
Length (m)	1.73 ± 0.09	1.68 ± 0.08	1.73 ± 0.09	1.76 ± 0.09	1.75 ± 0.09	<0.001
Race (%)						<0.001
White	96.1	94.3	95.8	97.1	97.1	
Black	1.0	1.0	0.8	0.6	1.4	
Asian	1.9	3.3	2.2	1.0	0.9	
Other	1.1	1.4	1.2	1.3	0.6	
Family history of CVD (%)	48.4	45.0	48.4	50.7	49.3	<0.001
History of CVD (%)	6	3.3	4.1	6.4	10.2	<0.001
SBP (mmHg)	125.5 ± 18.3	115.5 ± 14.8	122.7 ± 16.3	127.0 ± 16.0	136.7 ± 19.2	<0.001
DBP (mmHg)	73.4 ± 9.1	67.0 ± 7.2	71.6 ± 7.5	75.1 ± 7.8	79.7 ± 9.0	<0.001
MAP (mmHg)	92.2 ± 12.3	84.4 ± 9.6	90.0 ± 10.6	93.8 ± 10.3	100.6 ± 12.4	<0.001
Pulse pressure (mmHg)	52.2 ± 13.0	48.5 ± 11.2	51.1 ± 12.5	52.2 ± 12.2	56.9 ± 14.3	<0.001
Heart rate (bpm)	68.4 ± 10.0	65.0 ± 8.5	67.2 ± 9.5	69.3 ± 9.8	72.3 ± 10.6	<0.001
Use of AHD (%)	20.9	14.1	16.2	19.9	32.7	<0.001
Smoking (%)						<0.001
Never	29.6	37.6	32.9	28.9	20.0	
Former	41.8	39.2	40.7	41.7	47.2	
Current	27.3	21.7	26.3	29.4	32.8	
Alcohol use (%)						<0.001
None/hardly ever	23.0	25.5	22.7	20.8	23.4	
1–4/month	15.8	18.7	17.0	13.9	13.8	
2–7/week	35.2	37.2	35.2	36.2	32.7	
1–3/day	20.2	15.5	21.0	22.5	22.2	
>3/day	5.2	2.6	4.1	6.6	7.8	
Total cholesterol (mmol/l)	5.42 ± 1.0	5.1 ± 1.0	5.39 ± 1.05	5.53 ± 1.05	5.59 ± 1.04	<0.001
HDL cholesterol (mmol/l)	1.22 (1.04–1.43)	1.33 (1.15–1.54)	1.25 (1.06–1.47)	1.17 (1.00–1.38)	1.14 (0.97–1.35)	<0.001
Triglycerides (mmol/l)	1.10 (0.81–1.58)	0.90 (0.67–1.28)	1.06 (0.77–1.50)	1.22 (0.90–1.72)	1.30 (0.93–1.88)	<0.001
Use of LLD (%)	8.9	5.9	7.1	8.6	14.1	<0.001
History of diabetes mellitus (%)	2.4	1.3	1.9	2.1	4.3	<0.001
Serum glucose (mmol/l)	4.93 ± 0.92	4.72 ± 0.81	4.88 ± 0.91	4.94 ± 0.76	5.17 ± 1.10	<0.001
Serum kreatinine (μmol/l)	73.7 ± 19.8	68.5 ± 13.5	72.6 ± 18.98	75.1 ± 15.2	78.6 ± 27.3	<0.001
eGFR (CKD-EPI)	93.3 ± 15.8	96.5 ± 14.7	95.4 ± 15.3	93.7 ± 14.9	87.7 ± 74.5	<0.001
Urinary sodium excretion	145 ± 54	134.3 ± 48.0	143.1 ± 51.8	151.5 ± 56.0	152.6 ± 59.3	<0.001
Urinary albumin excretion	8.60 [6.06–15.1]	7.09 [5.49–10.83]	8.16 [5.95–13.3]	9.11 [6.37–14.8]	11.28 [7.06–26.92]	<0.001

Data presented as mean ± SD, or median [IQR] or percentage of the population for normally, skewed, or nominal data, respectively. Differences were tested using analysis of variance (ANOVA), or Kruskal–Wallis tests for continuous data and with χ^2 tests for categorical data. AHD, antihypertensive drugs; CKD-EPI, Chronic Kidney Disease-Epidemiology collaboration; CVD, cardiovascular disease; DBP, diastolic blood pressure; DPPI, digital pulse propagation index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LLD, lipid lowering drugs; MAP, mean arterial pressure.

The association between DPPI and mortality was not materially changed when the model was adjusted for SBP rather than MAP (Supplemental Table 2, http://links.lww.com/HJH/B279).

The association between $_{\log}$DPPI and mortality was notably modified by age, MAP, the use of antihypertensive drugs and smoking, but not by sex (Supplemental Fig. 1, http://links.lww.com/HJH/B279). However, effect modification by MAP or the use of antihypertensive drugs was no longer present when the model was adjusted for age ($P_{\text{interaction}} = 0.74$ and $P_{\text{interaction}} = 0.50$, respectively). When participants with a prior history of CVD were excluded, DPPI remained significantly associated with all-cause and cardiovascular mortality [fully adjusted model: hazard ratio 1.20 (1.05–1.37), $P = 0.007$ and 1.63 (1.33–1.99) per SD increase in $_{\log}$DPPI, $P < 0.001$, respectively]. $_{\log}$DPPI was not associated with noncardiovascular mortality after adjustment for HR, age sex, and body height [hazard ratio 1.07 (0.99–1.12), $P = 0.08$].

Association of the digital pulse propagation index with cardiovascular events

During follow-up, 272 (5.0%) participants experienced a CAD event and 99 (1.8%) experienced a cerebrovascular event. Results of Cox regression analysis are shown in Table 4. $_{\log}$DPPI was significantly associated with both CAD [hazard ratio per SD 1.54 (95% confidence interval 1.41–1.67), $P < 0.001$] and cerebrovascular events [hazard ratio 1.63 (1.43–1.87), $P < 0.001$] in models adjusted for HR. These associations remained after further adjustment for age, sex and body height [CAD events: hazard ratio 1.17 (1.05–1.32), $P = 0.009$; cerebrovascular events: hazard ratio 1.26 (1.06–1.49) per SD, $P = 0.0!$], but lost significance upon further adjustment for covariates.

Association of the digital pulse propagation index with heart failure

In total, 146 participants developed new onset heart failure during follow-up. Of these, 86 (1.6%) participants

TABLE 2. Univariable and multivariable determinants of log-transformed digital pulse propagation index

	Univariable		Multivariable	
	β	*P* value	β	*P* value
Age	0.386	<0.001	0.327	<0.001
Mean arterial blood pressure	0.482	<0.001	0.292	<0.001
Body height	0.228	<0.001	0.290	<0.001
Heart rate	0.241	<0.001	0.233	<0.001
Current smoking	0.098	<0.001	0.121	<0.001
Male sex	0.327	<0.001	0.068	<0.001
Waist circumference	0.314	<0.001	−0.050	<0.001
HDL cholesterol	−0.213	<0.001	−0.037	0.005
Triglycerides	0.240	<0.001		
24 h urinary albumin excretion	0.225	<0.001		
Use of antihypertensive drugs	0.179	<0.001		
eGFR (CKD-EPI)	−0.157	<0.001		
Total cholesterol	0.137	<0.001		
24-h urinary sodium excretion	0.118	<0.001		
History of cardiovascular disease	0.112	<0.001		
Use of lipid-lowering drugs	0.107	<0.001		
NT-proBNP	0.107	<0.001		
History of diabetes	0.063	<0.001		

Model 1: univariable analysis; model 2: multivariable model after stepwise backward elimination ($r^2 = 0.43$). CKD-EPI, Chronic Kidney Disease-Epidemiology collaboration; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal-pro brain natriuretic peptide.

developed HFrEF while 60 (1.1%) developed HFpEF. $_{log}$DPPI was associated with incident HFrEF [hazard ratio 1.81 (1.60–2.06), $P < 0.001$; Fig. 2] and incident HFpEF [hazard ratio 1.31 (1.04–1.63), $P = 0.019$]. The association between DPPI and new-onset HFrEF remained significant in the fully adjusted model [hazard ratio 1.32 (1.08–1.60), $P = 0.005$; Table 5], suggesting a 32% greater risk of incident HFrEF per SD increase in $_{log}$DPPI. The association with HFpEF was lost after further adjustment for covariates. After exclusion of participants with a prior history of CVD, $_{log}$DPPI remained associated with incident HFrEF [hazard ratio 1.56 (1.29–1.90), $P < 0.001$ per SD]. For HFrEF, the optimal cutoff value for DPPI was 6.1 m/s (AUC_{ROC}: 0.71; sensitivity: 63%; specificity: 72%). Adjustment for SBP instead of MAP did not significantly alter this association (Supplemental Table 2, http://links.lww.com/HJH/B279).

DISCUSSION

Large artery stiffness is widely recognized as a risk factor for cardiovascular and all-cause mortality [21]. Here, we demonstrate that the DPPI, derived from the peripheral PP waveform, is associated with a higher mortality risk in the general population. The association between DPPI and mortality was independent of traditional cardiovascular risk factors. In the fully adjusted model, one SD higher $_{log}$DPPI was associated with a 15% higher risk of mortality, while the risk of cardiovascular mortality was 43% higher for an SD higher $_{log}$DPPI. In addition, we demonstrate an association between the DPPI and incident HFrEF, with a 31% greater risk of incident HFrEF per SD of $_{log}$DPPI after adjustment for confounders. These independent associations all remained significant after exclusion of participants with a known history of CVD. Optimal cutoff values for DPPI were relatively consistent for all end points, ranging between 6.1 and 6.3 m/s, which corresponds to the cutoff between the third and fourth quartile of our study population.

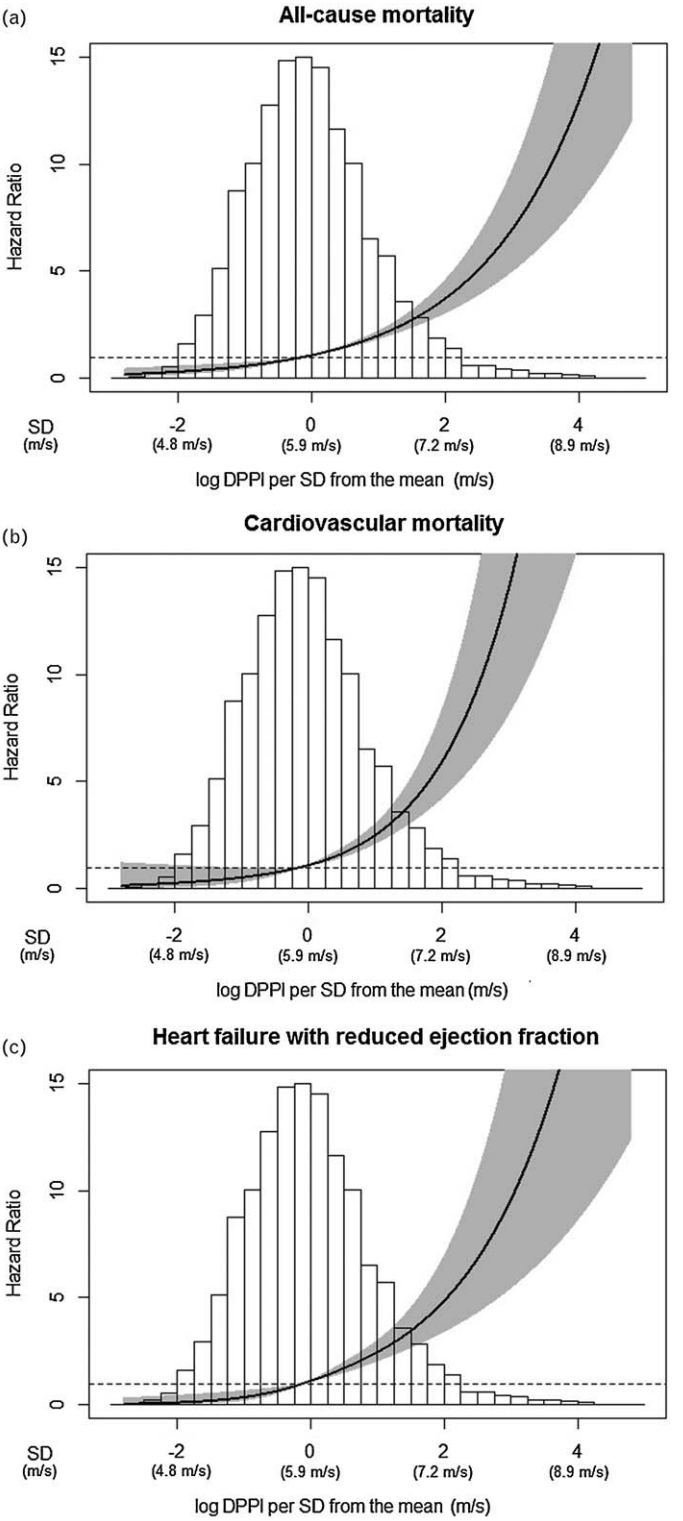

FIGURE 2 Spline curve of the association between log digital pulse propagation index and all-cause mortality (a), cardiovascular mortality (b), and heart failure with reduced ejection fracture (c) after adjustment for heart rate. The gray area represents the 95% confidence interval of the hazard ratio.

Pulse contour analysis has previously been shown to be reproducible with minimal intraobserver variation [22,23].

TABLE 3. Associations of digital pulse propagation index with all-cause and cardiovascular mortality

		Intermediate DPPI (Q3)	High DPPI (Q4)		$_{Log}$DPPI continuous		
	Low DPPI (Q1 + Q2)	HR (95% CI)	HR (95% CI)	*P* (trend)	HR (95% CI) per SD	*P*	Harrell's *C*
All-cause mortality, $n = 289$							
Model 1	1.0 (ref)	1.87 (1.57–2.24)	5.52 (4.13–7.38)	<0.001	1.67 (1.55–1.81)	<0.001	0.71
Model 2	1.0 (ref)	1.04 (0.75–1.7)	1.72 (1.24–2.39)	<0.001	1.19 (1.07–1.33)	0.002	0.82
Model 3	1.0 (ref)	1.10 (0.77–1.59)	1.63 (1.17–2.28)	0.002	1.14 (1.02–1.27)	0.025	0.83
Model 4	1.0 (ref)	1.09 (0.77–1.61)	1.65 (1.18–2.30)	0.002	1.14 (1.02–1.28)	0.024	0.84
Cardiovascular mortality, $n = 74$							
Model 1	1.0 (ref)	1.85 (1.25–2.75)	8.31 (4.55–15.16)	<0.001	1.95 (1.72–2.22)	<0.001	0.75
Model 2	1.0 (ref)	1.11 (0.74–1.66)	2.59 (1.36–4.95)	0.001	1.49 (1.27–1.76)	<0.001	0.88
Model 3	1.0 (ref)	1.51 (0.67–3.37)	2.66 (1.37–5.16)	0.002	1.41 (1.19–1.68)	<0.001	0.91
Model 4	1.0 (ref)	1.57 (0.70–3.54)	2.60 (1.33–5.08)	0.004	1.45 (1.22–1.73)	<0.001	0.92

CI, confidence interval; DPPI, digital pulse propagation index; HR, hazard ratio.

TABLE 4. Associations of digital pulse propagation index with fatal and nonfatal cardiovascular events

		Intermediate DPPI (Q3)	High DPPI (Q4)		$_{Log}$DPPI continuous		
	Low DPPI (Q1 + Q2)	HR (95% CI)	HR (95% CI)	*P* (trend)	HR (95% CI) per SD	*P*	Harrell's *C*
CAD events, $n = 227$							
Model 1	1.0 (ref)	2.03 (1.71–2.41)	4.43 (3.28–5.96)	<0.001	1.53 (1.41–1.67)	<0.001	0.68
Model 2	1.0 (ref)	1.29 (0.97–1.74)	1.93 (1.37–2.72)	<0.001	1.17 (1.05–1.32)	0.009	0.76
Model 3	1.0 (ref)	1.32 (0.92–1.91)	1.54 (1.06–2.25)	0.03	1.02 (0.90–1.17)	0.74	0.81
Model 4	1.0 (ref)	1.28 (0.88–1.85)	1.50 (1.03–2.18)	0.04	1.02 (0.89–1.16)	0.78	0.81
Cerebrovascular events, $n = 99$							
Model 1	1.0 (ref)	3.01 (2.29–3.96)	4.62 (2.76–7.74)	<0.001	1.63 (1.43–1.87)	<0.001	0.67
Model 2	1.0 (ref)	1.99 (1.49–2.66)	1.90 (1.07–3.36)	0.05	1.26 (1.06–1.49)	0.01	0.80
Model 3	1.0 (ref)	2.11 (1.14–3.54)	1.54 (0.86–2.76)	0.25	1.15 (0.96–1.38)	0.12	0.81
Model 4	1.0 (ref)	2.09 (1.18–3.69)	1.57 (0.87–2.83)	0.24	1.18 (0.98–1.43)	0.08	0.83

Model 1: association for log-transformed DPPI, adjusted for heart rate DPPI; model 2: model 1 + adjustment for age, sex, and body height; model 3: model 2 + adjustment for MAP, use of antihypertensive drugs, smoking, prior history of cardiovascular disease, and NT-proBNP; model 4: model 3 + adjustment for waist circumference, HDL cholesterol, triglycerides, history of diabetes, eGFR, urinary albumin excretion and urinary sodium excretion. CAD, coronary artery disease; CI, confidence interval; DPPI, digital pulse propagation index; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MAP, mean arterial pressure.

Previous cross-sectional studies have shown that the method may have added benefit in the stratification of CVD risk [12–14,22]. Our results extend these findings by showing that differences in DPPI relate to the long-term risk of mortality after adjustment for other risk factors, thus providing prospective epidemiological validation for this method.

In this cohort, higher DPPI was notably associated with the presence of traditional cardiovascular risk factors at baseline. In concordance with the pathophysiology of arterial stiffening, age, HR, and MAP were strong determinants of DPPI in a multivariable linear regression model [2,24]. Of note, greater body height was also independently associated with higher DPPI. Sex, waist circumference, smoking status, plasma HDL cholesterol and antihypertensive drug use were independently associated with DPPI, but contributed comparatively little to the regression model. In line with findings from the Framingham Heart Study, we found no independent association between arterial stiffness and either eGFR or albuminuria [25]. In total, the final linear regression model explained 43% of the variance in DPPI.

TABLE 5. Associations of digital pulse propagation index with new-onset heart failure

		Intermediate DPPI (Q3)	High DPPI (Q4)		$_{Log}$DPPI continuous		
	Low DPPI (Q1 + Q2)	HR (95% CI)	HR (95% CI)	*P* (trend)	HR (95% CI) per SD	*P*	Harrell's *C*
HFrEF, $n = 86$							
Model 1	1.0 (ref)	2.13 (1.51–3.01)	7.32 (4.15–12.94)	<0.001	1.81 (1.60–2.06)	<0.001	0.74
Model 2	1.0 (ref)	1.27 (0.89–1.81)	2.64 (1.43–4.87)	0.001	1.42 (1.20–1.68)	<0.001	0.83
Model 3	1.0 (ref)	1.33 (0.67–2.69)	2.16 (1.14–4.09)	0.013	1.29 (1.06–1.57)	0.010	0.89
Model 4	1.0 (ref)	1.34 (0.66–2.72)	2.26 (1.18–4.33)	0.009	1.32 (1.08–1.60)	0.005	0.91
HFpEF, $n = 60$							
Model 1	1.0 (ref)	1.03 (0.53–2.02)	1.84 (1.02–3.35)	0.06	1.31 (1.04–1.63)	0.019	0.59
Model 2	1.0 (ref)	0.79 (0.39–1.60)	0.90 (0.46–1.76)	0.76	0.98 (0.76–1.27)	0.89	0.82
Model 3	1.0 (ref)	0.80 (0.40–1.62)	0.81 (0.41–1.59)	0.55	0.91 (0.71–1.19)	0.51	0.85
Model 4	1.0 (ref)	0.86 (0.42–1.72)	0.84 (0.42–1.66)	0.61	0.94 (0.73–1.22)	0.65	0.86

Model 1: association for log-transformed DPPI, adjusted for heart rate; model 2: model 1 + adjustment for age, sex, and body height; model 3: model 2 + adjustment for MAP, use of antihypertensive drugs, smoking, prior history of cardiovascular disease, and NT-proBNP; model 4: model 3 + adjustment for waist circumference, HDL cholesterol, triglycerides, history of diabetes, eGFR, urinary albumin excretion, and urinary sodium excretion. CI, confidence interval; DPPI, digital pulse propagation index; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fracture; HR, hazard ratio; MAP, mean arterial pressure; NT-proBNP, N-terminal-pro brain natriuretic peptide.

Our results show that the DPPI is independently associated with mortality, and suggest that this association is driven by cardiovascular mortality. The DPPI was also strongly associated with HFrEF. However, the associations with cerebrovascular events and HFpEF were lost upon multivariable adjustment. When analyzed as a continuous variable, CAD was also not associated with DPPI after adjustment for confounders. However, we did observe a significantly higher hazard ratio for CAD for participants in the highest quartile of our cohort. The lack of a strong association with CAD is in line with a previous study showing that the DPPI is not associated with CAD identified by coronary angiography [13]. These observations may result from the fact that the DPPI is related to peripheral rather than aortic stiffness, unlike cfPWV [13]. Similarly, cerebrovascular events are more strongly associated with aortic stiffness than with peripheral arterial stiffness [26]. The significant association between cardiovascular mortality and DPPI but not (in continuous analysis) with coronary artery events or cerebrovascular events may suggest that the excess mortality risk in participants with high DPPI is mainly driven by deaths due to heart failure, although this could not be definitively clarified by our current data.

Several mechanisms have previously been proposed to explain the associations between arterial stiffness and mortality. For example, higher DPPI may be indicative of genetic and structural predisposition to cardiovascular risk [27]. In addition, associations have been reported between DPPI and markers of higher bone resorption and lower bone formation in patients with CKD stage 1–4, suggesting a link between the DPPI and vascular calcification [28]. Lastly, arterial stiffness may be linked to systemic inflammation [29–31]. Quantification of these and other processes impacting arterial ageing is likely to aid in the prediction of cardiovascular risk, as well as in the epidemiological and mechanistic study of CVD. Our study has a number of limitations. First, our study is observational in nature and therefore no conclusions can be drawn on causality. Second, by design, the study cohort includes a larger proportion of individuals with microalbuminuria than the general population [16]. Accordingly, we have adjusted our analyses for albuminuria. Third, our cohort consists primarily of whites due to the geographical area of recruitment; future studies on the role of the DPPI in nonwhite populations are warranted. Fourth, our study made use of a single 15-min arterial stiffness measurement at baseline even though arterial stiffening is a dynamic process, the rate of which may vary over time. In the absence of repeated measurements, this variability is unaccounted for, which may lead to underestimation of the strength of associations due to regression dilution bias. Fifth, the method used to derive stiffness from the digital pressure pulse is indirect. As such, the DPPI may not reflect true large artery stiffness due to confounding by properties of peripheral vessels. Sixth, cause of death in this cohort was classified using the primary cause of death as reported on patients' death certificate. However, the reported cause of death may not properly reflect the true cause of death for all patients. On the contrary, informed consent for this study did not allow for a full review of medical records to further clarify cause of death. Lastly, the use of patient height to calculate an index expressed in meters per second is relatively imprecise, and might contribute to imprecision in the DPPI. This is reflected by the finding that height remained a determinant of the DPPI in linear regression analysis. However, inclusion of height in our survival analysis did not materially alter our results. Lastly, in this study, pulse contour analysis was performed using the digital arterial pressure waveform. This methodology is different from DVP, which has been used in several previous studies [10,11]. Although these different waveforms may be relatable to each other through a generalized transfer function, they are not identical and may convey different information. To our knowledge, arterial pressure-based waveform analysis has not been correlated with cfPWV, the current standard to quantify arterial stiffness.

In conclusion, higher DPPI corresponded closely with the presence of known causal risk factors for CVD in this large, well characterized general population-based cohort. Moreover, DPPI was independently associated with incident systolic heart failure, all-cause and cardiovascular mortality after adjustment for these risk factors. However, DPPI was not independently associated with risk of CAD events or cerebrovascular events. Further validation studies should confirm whether this accessible marker of arterial stiffness has value in risk stratification for these end points, and should define the position of DPPI in comparison with other available methods to determine vascular stiffness.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Abajobir AA, Abbafati C, Abbas KM, Abd-Allah F, Abera SF, Aboyans V, *et al*. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390:1151–1210.
2. Mattace-Raso FUS, Hofman A, Verwoert GC, Wittemana JCM, Wilkinson I, Cockcroft J, *et al*. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J* 2010; 31:2338–2350.
3. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, *et al*. Arterial stiffness and cardiovascular events the Framingham Heart Study. *Circulation* 2014; 121:505–511.
4. Hansen TW, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, *et al*. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation* 2006; 113:664–670.
5. Wang KL, Cheng HM, Sung SH, Chuang SY, Li CH, Spurgeon HA, *et al*. Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular mortalities: a community-based study. *Hypertension* 2010; 55:799–805.
6. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, *et al*. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well functioning older adults. *Circulation* 2005; 111:3384–3390.
7. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness. A systematic review and meta-analysis. *J Am Coll Cardiol* 2010; 55:1318–1327.
8. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, *et al*. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006; 27:2588–2605.
9. Millasseau SC, Ritter JM, Takazawa K, Chowienczyk PJ. Contour analysis of the photoplethysmographic pulse measured at the finger. *J Hypertens* 2006; 24:1449–1456.

10. Millasseau SC, Kelly RP, Ritter JM, Chowienczyk PJ. Determination of age-related increases in large artery stiffness by digital pulse contour analysis. *Clin Sci* 2002; 103:371–377.
11. Millasseau SC, Guigui FG, Kelly RP, Prasad K, Cockcroft JR, Ritter JM, *et al*. Noninvasive assessment of the digital volume pulse. Comparison with the peripheral pressure pulse. *Hypertension* 2000; 36:952–956.
12. Clarenbach CF, Stoewhas AC, Van Gestel AJ, Latshang TD, Lo Cascio CM, Bloch KE, *et al*. Comparison of photoplethysmographic and arterial tonometry-derived indices of arterial stiffness. *Hypertens Res* 2011; 35:228–233.
13. Vakalis K, Bechlioulis A, Naka KK, Pappas K, Katsouras CS, Michalis LK. Clinical utility of digital volume pulse analysis in prediction of cardiovascular risk and the presence of angiographic coronary artery disease. *Artery Res* 2015; 9:33–39.
14. Gunarathne A, Patel JV, Hughes Ea, Lip GYH. Measurement of stiffness index by digital volume pulse analysis technique: clinical utility in cardiovascular disease risk stratification. *Am J Hypertens* 2008; 21:866–872.
15. Salvi P, Magnani E, Valbusa F, Agnoletti D, Alecu C, Joly L, *et al*. Comparative study of methodologies for pulse wave velocity estimation. *J Hum Hypertens* 2008; 22:669–677.
16. Pinto-Sietsma SJ, Janssen WM, Hillege HL, Navis G, De Zeeuw D, De Jong PE. Urinary albumin excretion is associated with renal functional abnormalities in a nondiabetic population. *J Am Soc Nephrol* 2000; 11:1882–1888.
17. Imholz BP, Wieling W, van Montfrans GA, Wesseling KH. Fifteen years experience with finger arterial pressure monitoring: assessment of the technology. *Cardiovasc Res* 1998; 38:605–616.
18. Brouwers FP, de Boer RA, van der Harst P, Voors AA, Gansevoort RT, Bakker SJ, *et al*. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. *Eur Heart J* 2013; 34:1424–1431.
19. Joosten MM, Gansevoort RT, Mukamal KJ, van Der Harst P, Geleijnse JM, Feskens EJM. Urinary and plasma magnesium and risk of ischemic heart disease. *Am J Clin Nutr* 2013; 97:1299–1306.
20. Fluss R, Faraggi D, Reiser B. Estimation of the Youden index and its associated cutoff point. *Biom J* 2005; 47:458–472.
21. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, *et al*. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; 34:2159–2219.
22. Sollinger D, Mohaupt MG, Wilhelm A, Uehlinger D, Frey FJ, Eisenberger U. Arterial stiffness assessed by digital volume pulse correlates with comorbidity in patients with ESRD. *Am J Kidney Dis* 2006; 48:456–463.
23. Woodman RJ, Kingwell BA, Beilin LJ, Hamilton SE, Dart AM, Watts GF. Assessment of central and peripheral arterial stiffness: studies indicating the need to use a combination of techniques. *Am J Hypertens* 2005; 18:249–260.
24. Palombo C, Kozakova M. Arterial stiffness, atherosclerosis and cardiovascular risk: pathophysiologic mechanisms and emerging clinical indications. *Vascul Pharmacol* 2016; 77:1–7.
25. Upadhyay A, Hwang SJ, Mitchell GF, Vasan RS, Vita JA, Stantchev PI, *et al*. Arterial stiffness in mild-to-moderate CKD. *J Am Soc Nephrol* 2009; 20:2044–2053.
26. Tsuchikura S, Shoji T, Kimoto E, Shinohara K, Hatsuda S, Koyama H, *et al*. Central versus peripheral arterial stiffness in association with coronary, cerebral and peripheral arterial disease. *Atherosclerosis* 2010; 211:480–485.
27. Laurent S, Boutouyrie P, Lacolley P. Structural and genetic bases of arterial stiffness. *Hypertension* 2005; 45:1050–1055.
28. Manghat P, Souleimanova I, Cheung J, Wierzbicki AS, Harrington DJ, Shearer MJ, *et al*. Association of bone turnover markers and arterial stiffness in predialysis chronic kidney disease (CKD). *Bone* 2011; 48:1127–1132.
29. Abramson JL, Weintraub WS, Vaccarino V. Association between pulse pressure and C-reactive protein among apparently healthy US adults. *Hypertension* 2002; 39:197–202.
30. Mahmud A, Feely J. Arterial stiffness is related to systemic inflammation in essential hypertension. *Hypertension* 2005; 46:1118–1122.
31. de Boer SA, Hovinga-de Boer MC, Heerspink HJL, Lefrandt JD, van Roon AM, Lutgers HL, *et al*. Arterial stiffness is positively associated with 18F-fluorodeoxyglucose positron emission tomography-assessed subclinical vascular inflammation in people with early type 2 diabetes. *Diabetes Care* 2016; 39:1440–1447.